Amendment to Sequence Listing:

The attached sheets include a Sequence Listing of Factor VIII. Additional, a computer diskette is included herewith including the Sequence Listing of Factor VIII in computer readable format (CRF), and being in ASCII format. Both the attached sheets and the CRF include the previously submitted sequence information and the currently submitted Factor VIII sequence listing, the latter being listed as SEQ ID No. 4.

Attachment: **SEQUENCE LISTING OF FACTOR VIII**

Enclosure: **Diskette of SEQUENCE LISTING OF FACTOR VIII in ASCII format.**

Submission of Drawings:

The attached sheets of drawings include Figs. 1-5 corresponding to the drawings of the PCT application, believed to have been originally filed with the present U.S. application and subsequently lost.

Attachments: Five (5) Sheets of Drawings

REMARKS

This Amendment and Response is submitted in reply to the Office Action mailed on November 18, 2005, and accompanies a Petition to Revive / Withdraw Holding of Abandonment. No new matter has been added by any of the amendments or submissions made herein.

The specification was objected to as lacking an Abstract. Previously, an Abstract from the corresponding PCT application was submitted. However, such submission was found not to be in accordance with PTO rules. Accordingly, the specification is amended herein to provide an Abstract. It is noted that the submitted Abstract differs from the PCT abstract in minor respects in order to conform to the USPTO's 150 word rule.

Sequence disclosures that are encompassed by 37 CFR §§1.821 through 1.825 are contained in the application. Appropriate amendment has been made to the specification regarding these sequences. Additionally, the sequence listing of Factor VIII, as known in the prior art, has been provided herewith in text form and in computer readable format (ASCII), as directed in the Office Action. As required by 37 CFR §1,821(f), the sequence listing information recorded in computer readable form is identical to the written sequence listing. It is noted that the International Search Report of the PCT phase of the present application lists WO94/11013, Applicant Duke University, which states "The DNA sequences for human factor VIII and human factor V, the locations of introns and exons, and the sequences of the intron-exon junctions are known. *See, e.g.,* L. Cripe et al., *Bicohem.* 31, 3777 (1992)." Therefore, at least for this reason, the submission of the sequence listing is not new matter.

Due to missing figures, drawing sheets from the corresponding PCT application from which the present application derives are hereby provided.

The disclosure is objected to for lack of a recitation of Figures 3 A-D. It is noted that the paragraph beginning "Figure 3:" on page 15, line 19, is followed by a paragraph, line 23, *et seq.*, intended to describe Figures 3 A-D. Nonetheless, both paragraphs have been amended to more clearly refer to and distinguish between the Figures 3 A-D. It is noted that, as the paragraph beginning on line 19, is underlined in the original, double-underlining is utilized to show changes made thereto. The amendments are supported by the paragraphs, page 15, lines 19-29, and the Figures themselves.

Claims 86-123, 141-143, and 151-154 are pending in this application. Claims 86-109, 117-120, and 151-154 are allowed. Claims 110-116, 121-123, and 141-143 are rejected.

Claim 110 has been rejected as indefinite under 35 USC §112 for lack of antecedent basis. Claim 110 has been *marked* to show changes and is, thus, listed as currently amended. Previously, strike-through was used on the number "104"; however, the line was not visible due to the "4" itself. Accordingly, double-brackets have been used to indicate the deleted text.

The Office Action states that claims 111-116, 121-123, and 141-143 are rejected under 35 USC §101 as not being supported by either a specific or substantial asserted utility or well-established utility, and that claims 114-116, 121-123, and 141-143 are added to this rejection as it is not shown that peptides or analogs are useful as inhibitors. The Office Action further states that claims 111-116, 121-123, and 141-143 are also rejected under 35 USC §112 as one skilled in the art would not know how to use the claimed invention.

Applicants note the statement in the Office Action relevant to peptide competitive inhibitors: "it is submitted that this is in fact deduction: the inventors have not demonstrated it." Contrary to the presumption, the Applicants (however inartfully) are indicating that this fact, indeed, would be recognized by one skilled in the art. More particularly, it appears as though there is some misunderstanding as to the meaning of the peptides as competitive inhibitors. The catalytic antibody has binding sites which, when bound with the Factor VIII, result in cleaving the Factor VIII, and then releasing the Factor VIII fragments. The peptides act by binding with the catalytic antibody binding sites (and not to the Factor VIII) so that access to the binding sites is prevented for Factor VIII, the result of which being the Factor VIII is not cleaved. It is in this manner that the peptides or analogues are competitive inhibitors.

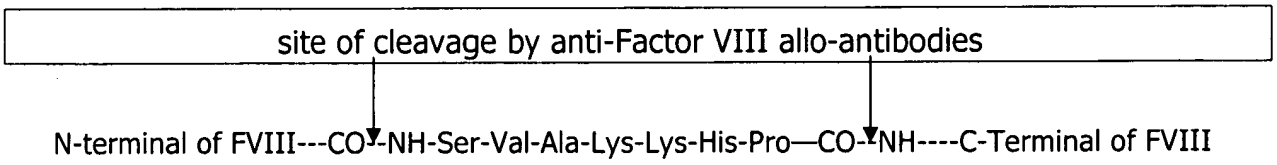
Turning now to the rejections detailed in the Office Action for these claims, the specification makes clear what the utility of the claimed sequences is. For instance, page 6, line 17, *et seq.*, states "the present invention provides an anti-body Factor VIII allo-antibody-catalysed Factor VIII degradation inhibitor." Continuing, "this inhibitor inhibits cleavage of the scissile bonds . . . of the Factor VIII molecule. More preferably still, this inhibitor is characterized in that it comprises a peptide or non-peptide analogue of the amino acid sequence," at which point the amino acids of claims 111-113 are listed. Accordingly, it should be abundantly clear what is the utility of the claimed amino acids of these claims, as well as of the claims dependent therefrom.

Furthermore, this utility and benefit is reinforced by the language of the claims themselves. Resonating with the above remarks, as a mere example of points discussed within the specification, exemplary claim 114 states a "peptide or non-peptide analogue of an amino

acid sequence of claim 111, which is capable of inhibiting any site in the Factor VIII molecule which is susceptible to being lysed by an anti-Factor VIII allo-antibody."

Therefore, as described in the previous response, when one of said peptide sequences is added to the Factor VIII/allo-antibody mix then a "Competitive Inhibition", a term which is well-understood by the person of ordinary skill in the art, ensues; it is due to the competition of these peptides with the corresponding sequences of the Factor VIII molecule to be cleaved, that they thus "prevent" or "protect" the Factor VIII from being cleaved by the allo-antibody. The isolated peptide sequences do not have the cleavage site which is recognised by the allo-antibody, nor do the isolated peptide sequences have bonds which are susceptible to being cleaved by the allo-antibody, since these isolated peptide sequences are merely the sequences as from the C-terminal of the cleavage site,

The Office Action suggests rejections based on utility would be overcome if the sequence and site of cleavage were of the record. As noted above, the sequence is being submitted herewith. Though presented in the previous response, the isolated amino acid sequences in question are regions of cleavage of Factor VIII by the allo-antibody of the claims. Namely, said sequences are those found as from the C-terminal of the site of cleavage of the Factor VIII molecule by the anti-Factor VIII allo-antibodies, downstream in the direction of the C-terminal of the Factor VIII amino acid sequence, as representatively shown here:



In light of the above discussion, it is believed that utility is established. Therefore, the rejection for one skilled in the art not knowing how to use the claimed invention is believed moot. In support of this, it is noted that both the manner of use and the benefit/utility of the claimed inventions are described as the basis of the application, throughout the specification and disclosure.

Claims 111-113 are rejected under 35 USC §102 as being anticipated by Ill, et al. (A), Lollar, et al. (B), or Voorberg (C), as detailed in the previous office action. The Office Action notes that amending the claims to include "consisting of" language would overcome the rejection. Accordingly, each of claims 111-113 are amended as directed, with thanks to the Examiner.

It is believed that each rejection and objection is successfully overcome. Accordingly, Applicants respectfully request reconsideration of the patentability of claims 110, 111-113, 121-123, and 141-143, that the claims be deemed allowable at this time, and that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

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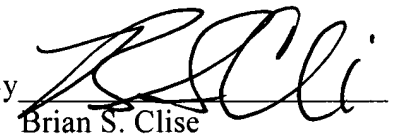
By 
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